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re patent application of:

Nielsen et al.

Serial No.: **08/319,411** Group No.: **Not yet assigned**

Filed: **October 6, 1994** Examiner: **Not yet assigned**

For: **PROTEIN NUCLEIC ACID CONJUGATES**

I, Michael P. Streher, Registretion No. 38,325 certify that this correspondence is being deposited with the U.S. Postal Service "Express Mail Post Office to Addressee" service and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231 "Express Mail" Label No. TB700312767US

Date of Deposit - June 14, 1995

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Sir:

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

(xx) In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, no additional fee is required.

( ) In accordance with §1.97(c), this Information Disclosure Statement is being filed after the period set forth in §1.97(b) above but before the mailing date of either a Final Action under §1.113 or a Notice of

Allowance under §1.311, therefore:

( ) Certification in Accordance with §1.97(e) is attached; or

( ) The fee of $**210.00** as set forth in §1.17(p) is attached.

( ) In accordance with §1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under §1.113 or a Notice of Allowance under §1.311 but before the payment of the Issue Fee, therefore included are: Certification in Accordance with §1.97(e); Petition Requesting Consideration of the Information Disclosure Statement; and the fee of $**130.00** as set forth in §1.17(i)(1).

(xx) Copies of each of the references listed on the attached Form PTO-1449 are enclosed herewith with the exception of AA, AM, AW, BS, CE, CM, DT, EN, EO, FQ, FU, GZ, HA, HB, HC, HD, and HE. In view of the voluminous nature of these publications, and the likelihood that the Examiner may have a copy of these publications available to him or her, copies have not been included herewith. However, if the Examiner does not have a copy available, Applicant will endeavor to supply one at the Examiner's request.

( ) In accordance with §1.98(d), copies of some or all of the references listed on the attached Form PTO-1449 are not enclosed herewith because they were previously cited by or submitted to the Patent and Trademark Office in prior application Serial No. for which a claim for priority under 35 U.S.C. §120 has been made in the instant application.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050. This form is submitted in triplicate.

The relevance of those listed references which are not in the English language is as follows:

DG König and Geiger, "Racemisierung bei Peptidsynthesen", *Chem. Ber.* **1973**, *103*, 2024-2033.

teaches that 3-hydroxy-4-oxo-3, 4-dihydro-1,2,3-benzotriazine as additive to DCCD decreases racemization in the DCCD-method to a minimum, compared with a series of N-hydroxy-compounds. Konig and Geiger also teaches that it is possible to prepare the intermediate activated esters without racemization. Addition of weak tertiary bases has a favourable effect on the yield and racemization in the preparation of N-acylpeptide-N-hydroxysuccinimide esters by the DCCD-method.

DH König and Geiger, "Eine Neue Methode Zur Synthese Von Peptiden: Aktivierung Der Carboxylgruppe Mit Dicyclohexylcarbodiimid Und 3-Hydroxy-4-oxo-3.4-dihydro-1.2.3-benzotriazin", *Chem. Ber.* **1973**, *103*, 2034-2040.

teaches that 3-Hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine is a suitable additive in the DCCD method for peptide synthesis. Konig and Geiger further find that it is possible to prepare the activated esters of N-protected peptides and amino acids with this compound without racemization.

DM Kupryszewski, "O Estrach Chlorofenylowych Aminokwasow. II. Synteza Peptydow Poprzez Aminolize Aktywnych Estrow 2,4,6-Trojchlorofenylowych N-Chronionych Aminokwasow", *Rocz. Chem.* **1961**, *35*, 595-600.

teaches a method for the synthesis of N-protected peptide esters by aminolysis of active N-protected aminoacid 2,4,6-trichlorophenyl esters.

EY Pless *et al.*, "Über die Geschwindigkeit der Aminolyse von Verschiedenen Neuen, Aktivierten, N-geschützten α-Aminosäure-phenylestern, insbesondere 2,4,5-Trichlorphenylestern) *Helv. Chim. Acta* **1963**, *46*, 1609-1625.

teaches that the presence of a gem-dimethyl group of C-4 gives rise to a marked improvement in the yield of the cyclic 11B, 19-cyclo-11-hydroxy compounds from 11-keto steroids.

FL Sieber and Iselin, "77. Selektive Acidolytische Spaltung von Aralkyloxycarbonyl-Aminoschutzgruppen", *Helv. Chem. Acta*. **1968**, *51*, 614-622.

investigated the acidolytic cleavage of a series of new N-aralkyloxycarbonyl protecting groups.

Date: June 14, 1995

Signature
Michael P. Straher
Registration No. **38,325**

WOODCOCK WASHBURN KURTZ
MACKIEWICZ & NORRIS
One Liberty Place - 46th Floor
Philadelphia, PA 19103
(215) 568-3100